ISSUE BRIEF

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# Considerations for Summary Review of Supplemental NDA/BLA Submissions in Oncology

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## Introduction

To add a new indication to the labeling of an approved drug in the United States, a sponsor must obtain approval of a supplemental new drug application (sNDA) or supplemental biologics license application (sBLA). A supplemental application typically parallels the content of an original NDA/BLA application, and includes the "raw" datasets (patient level data extracted from case reports and analysis files that include created variables) from clinical trials and efficacy and safety analyses derived from these data by the sponsor to support the proposed new indication. In addition to summary documents for efficacy and safety, and clinical study reports, additional patient-level details are provided via case report forms and narratives. When evaluating supplemental applications, FDA medical and statistical reviewers review the sponsors' analyses presented in the summary documents and clinical study reports, but also typically engage in detailed reviews of individual patient data and may perform additional analyses using the raw datasets to confirm the sponsor's results and, in some cases, address other questions of interest not presented by the sponsor. These additional reviews and analyses can consume considerable time and resources and may not always add value to the regulatory determination of safety and efficacy, particularly in cases where the supplemental application shows a large magnitude of benefit on an accepted efficacy endpoint in a context where the existing safety profile of the drug is well known from previous submissions, real-world experience, and post-marketing safety data.

If there were criteria to enable FDA to identify a subset of sNDAs in which these additional analyses could be more targeted, or deemed unnecessary, increased FDA resources could be directed to activities such as expedited reviews of new investigational drugs for conditions with high unmet medical need, ongoing surveillance of existing products, and collaborative development of new initiatives to support

innovative drug development. More efficient use of resources could also potentially shorten sNDA review periods, which may encourage more submissions of supplemental applications for new indications, thereby providing patients, providers and payers with optimal information about the use of a drug. Considering these potential advantages, we will explore the concept of a "summary review" in which FDA focuses their review on the submitted clinical study report and sponsor analyses for qualifying efficacy supplements where regulatory uncertainty about data quality and efficacy is low in the setting of an approved product with robust existing safety database. Similar review approaches are used by other global regulatory authorities, including the European Medicines Agency and Health Canada, to support new and supplemental applications, although these agencies may delve deeper into the raw data when necessary and may place weight on the fact that full datasets are often reviewed by the FDA.

Initially, this program would be limited to particularly straightforward supplemental applications (Table 1) -- those in which there is clear evidence of drug efficacy based on an established endpoint and a large, existing safety database in reasonably comparable patient populations. This type of review would not be appropriate for applications where a more in depth review would be necessary including accelerated approvals or their post-marketing confirmatory trials, applications based on novel endpoints, or indications in neo-adjuvant or prevention settings. High assurance in the fidelity and comprehensiveness of the derived data, based on the quality of previous submissions, would also be a consideration for qualification.

Currently, FDA statistical reviewers conduct validation checks of submitted datasets to ensure the integrity of the analysis files from which the efficacy and safety results reported by the sponsor were generated. These checks focus on file construction and variable creation, with emphasis on the key efficacy and safety outcome variables. Additional checks may be performed to look for data quality issues and, in the extreme case, fraudulent data. In addition to these data validation analyses, FDA statistical and medical reviewers typically conduct data analyses to (i) replicate the sponsor's primary and key secondary findings and investigate the robustness of those findings, and (ii) explore other questions of interest possibly not explored by the sponsor as part of the submission, e.g., to investigate other safety events or estimate benefit and risk for other subgroups. This practice of FDA's conducting data validation checks and additional data analyses require the sponsor to submit datasets. Of interest here is whether these analyses are necessary for all supplemental applications, or whether they can be replaced in some cases with some combination of data and analysis file audits and analyses requested by the FDA for the sponsor to conduct as part of their review. For this to be a viable approach, we must explore whether any risk to patient outcomes may be introduced by eliminating, reducing, or modifying the current U.S. regulatory practice of routinely reviewing the raw data for drugs with already well-defined safety and efficacy in other disease settings and develop strategies to manage foreseeable risk.

**Re-analysis of sNDA raw data does not significantly alter the interpretation of a drug's safety profile**

To investigate the potential impact of the proposed approach on the quality of regulatory decisions, this working group performed the following: 1) evaluated the US labels (United States product inserts; USPIs) for Afinitor, Sutent, Gemzar, and Alimta to determine how safety labeling changed over time as new indications were added; 2) compared USPIs for these same agents to EU labels (summary of product characteristics; SmPCs) and Canadian labels (product monographs; PMs) to determine if the different

approach to review of supplemental applications resulted in significant differences in safety findings. These drugs were chosen because each has been on the market for several years and each has received approval in a variety of different disease settings: Afinitor was initially approved in 2009 for treatment of renal cell carcinoma (RCC) and subsequently received traditional approval for treatment of hormone receptor-positive breast cancer (HR+ BC) and pancreatic neuroendocrine tumors (PNET); Sutent was initially approved in 2006 for treatment of both gastrointestinal stromal tumors (GIST) and RCC, and was later approved for PNET; Gemzar was initially approved in 1996 and is indicated for treatment of breast cancer, ovarian cancer, non-small cell lung cancer (NSCLC), and pancreatic cancer; Alimta was initially approved in 2004 for treatment of mesothelioma and subsequently received approval for treatment of metastatic nonsquamous NSCLC.

These evaluations found that review of full datasets for each new indication resulted in no significant change to the existing safety profiles described in US labels. Similarly, they did not find significant differences between US, EU, and Canadian labels despite the differences in review approaches. Most differences in adverse event (AE) labeling between the different agencies could be attributed to slight differences in interpretation or labeling requirements, rather than access to data or lack thereof. One exception was Sutent, for which the SmPC included a more extensive list of AEs than the USPI, mainly because the EMA expected all AEs be reported regardless of frequency. Some rare, serious AEs were added to US labels over time as a result of post-marketing surveillance rather than clinical trials, and thus these differences were not attributed to the submission and review of raw datasets. In some cases, revisions to AEs reported in USPIs could be attributed to disease-specific safety issues. For example, the analysis of the Afinitor label over time found no new AE terms that appeared for a specific indication, or emerged over time based on sNDA application; however it did find some AEs in which the incidence was more in one indication than the other and could be attributed to that indication. For example, although incidence of diarrhea for all indications was the second most common GI disorder, it was considerably higher in PNET than the other two indications, likely due to more GI involvement in PNET disease. The results of these analyses are consistent with a recent publication which analyzed the reasons for which some drugs fail to achieve FDA approval and found only 2 examples out of 151 applications which failed to receive approval upon first submission where missing data were responsible for this failure.[1]

**Proposed components of a "Summary Review" program**

The concept of a "Summary Review" is to leverage existing knowledge of a drug's efficacy and safety to increase the efficiency of the sNDA review by focusing the clinical and statistical review on the clinical study report rather than in-depth analyses of submitted datasets. Table 2 outlines a proposal for a potential pilot "summary review" program. Sponsors and the FDA would determine at the pre-sNDA meeting whether a particular submission is eligible for "summary review" and, if so, exactly what would be submitted to and reviewed by FDA. For quality control purposes, sponsors may need to submit a random sample of patient-level case report data, narratives and/or analysis files according to a validation plan developed by FDA reviewers and requested of the sponsor following their preliminary review of the

[1] Sacks LV, Shamsuddin HH, Yasinskaya YI, Bouri K, Lanthier ML, Sherman RE. *Scientific and regulatory reasons for delay and denial of FDA approval of initial applications for new drugs*, 2000-2012. Journal of the American Medical Association. 2014;311(4):378-84. Epub 2014/01/23.

summary reports. Sponsors would also have to be prepared to provide additional data and analyses if needed to prevent any potential delay in the review.

Because it is not yet clear exactly what should be encompassed in a summary review, we propose that this program utilize a phased approach. In the pilot phase, the FDA would work with participating companies which would submit only the clinical study reports and analysis files, but hold the raw data elements (patient level data extracted from the case report forms) at the ready, to be submitted if needed. This approach would enable reviewers to assess whether there are data elements beyond the clinical study reports and analysis files that are routinely needed and also to determine how efficiently reviewers can obtain what they need through information requests. FDA reviewers would then report on what would constitute the essential data elements for a summary review in these cases, as well as those elements that are not necessary. The program would then transition to a system where only the clinical study reports are submitted. It may be that a random sample of patients, raw data items, and derived variables to support a QA/QC audit of the database would be integrated in the submission. As a future step in piloting this summary review approach, further streamlining of the submission such as removing the requirement to submit case report forms or patient narratives, could be considered, as appropriate.

It is envisioned that this program could be complimentary to ongoing efforts to streamline the actual data collection for supplemental applications. As an outgrowth of the 2008 and 2009 Conferences on Clinical Cancer Research co-hosted by Friends of Cancer Research and the Brookings Institution, ASCO and FDA working groups have been developing recommendations to streamline the collection of adverse event and toxicity data for supplemental applications.[2] These efforts led to the 2012 release of an FDA Draft Guidance for Industry, *Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations*, describing appropriate circumstances for targeted safety data collection, safety data that could be abbreviated or not collected in these circumstances as well as data that should always be collected.[3] For example, this guidance describes non-serious adverse events that are not associated with drug discontinuation as a data element that should be well-characterized for drugs which have already received approval for prior indications and therefore, collection of these adverse events in additional indications would add little to the understanding of the drug's safety profile.

## Conclusion

This program is intended to help ensure that all resources devoted to the development of oncology products, be they federal or private, contribute meaningfully to the well-being of patients, and at the same time maintain the integrity and quality of the regulatory review process and decision-making. The proposal described here, and parallel efforts to streamline safety data collection, recognize that when sponsors and the FDA already have significant understanding about a drug, more targeted data collection and less comprehensive submissions may suffice. The time and resources currently spent collecting, preparing for submission, and reviewing data that do not contribute to the quality of the submission or the regulatory review and decision, could be better spent on projects with tangible benefit for patients. This

[2] Abrams J, Erwin R, Fyfe G, Schilsky RL. *Data submission standards and evidence requirements*. The oncologist. 2010;15(5):488-91. Epub 2010/05/22.

[3] FDA. *Guidance for Industry: Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations.* 2012; Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291158.pdf.

focus on ensuring that all efforts meaningfully contribute to improving patient care and well-being is likely to help stimulate labeling supplements for approved cancer therapies (thereby helping to ensure that patients, providers and payers are fully and accurately informed about optimal use of therapies) and has implications beyond supplemental indications for cancer therapies.

*Table 1: When is Summary Review Appropriate?*

| **Eligible Supplements** | **Not Eligibile for Summary Review** |
|---|---|
| * Approved drug with large safety database | * Prevention, adjuvant, or neo-adjuvant trials |
| | * Accelerated approvals or their post-marketing confirmatory trials |
| * No new concerning safety signal | |
| * Established, objective primary endpoint<br>- Overall survival<br>- Very large progression-free survival | * Unestablished or novel endpoints for the indication |
| | * Unclear risk:benefit - advisory committee may be needed |
| * Robust effect, internal consistency and clear risk:benefit | * Novel combinations depending on additive toxicities or drug-drug interactions |

*Table 2: Proposed Elements of Summary Review*

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|---|
| * Review clinical study reports (CSR) and sponsor analyses for carefully selected sNDAs |
| * Eligibility determined by FDA Office of Hematology and Oncology Products at pre-sNDA meeting |
| * Pilot phase will determine if any raw data elements are still submitted |
| * Validation sample for QC |
| * Potential shortened review period |